Pain and Analgesic Tracts

Introduction

Just as there is a sensory system with a primary somatosensory cortex and a paired motor system (one signal up, one signal down) within the primary motor cortex, there is a similarly paired pain system with a pain center (sensory) in the brainstem and analgesia tract (motor) with an analgesia center in the brainstem. And although the pain tract also goes up to the primary somatosensory cortex, this pain and analgesic pairing does not. The pain tract is going to introduce a new neurotransmitter we haven't yet discussed—substance P—and the analgesic tract will introduce a new set of neurotransmitters—collectively called endorphins—and receptors—opioid receptors κ, μ, and δ.

An **opiate** is an endogenous compound that is made by human bodies and activates **opioid receptors**. Opiates are also a medication class that is naturally derived from the poppy flower—opium. **Opium** (the drug), morphine (the medication), and codeine (also found in poppies in small quantities) are all opiates. All other compounds that activate opioid receptors are **opioids**. Although this distinction rarely matters in clinical practice, as you will see in this lesson, mechanisms of tolerance may actually draw a distinction.

We start with the pain tract and a detailed view of the lateral spinothalamic tract's (STT) mechanism, then transition into the analgesia tract, the motor arm paired with the pain tract that helps modulate the pain response. Then we transition into the cellular physiology and second messenger systems of the analgesic tract. We close with mandatory content about opiate medications and reversal agents. Finally, this lesson includes some of the proposed mechanisms by which tolerance develops, and although the understanding is not yet elucidated, it portrays what is possible.

The Pain Tract

We discussed how the STT can carry both pain and temperature. This is true. But we left a lot of the discussion out of the spinal cord lessons because we wanted you to focus on laterality and identifying lesions. Now, we're going to talk about axon conduction velocity as it relates to pain and tell you more truth about the STT.

Pain is sensory, with fibers ascending the spinal cord. The neural crest-derived peripheral sensory neuron has its cell body in the ganglion outside the spinal column. The sensory signal travels up its bifurcated axon, which immediately synapses onto a second-order neuron at the level it enters the spinal cord. The second-order neuron has an axon that crosses the midline at the same spinal level and ascends the lateral STT. That's all review. The first thing we add on, now, is that the STT is way more than just that tract. What we've been calling STT is actually a combination of neuron types, and it projects not only to the thalamus but also all over the brainstem.

The axons of sensory neurons in the dorsal root ganglia can be broadly separated into three categories—heavily myelinated type A fibers, lightly myelinated type B fibers, and unmyelinated type C fibers. We go into detail on these types in the lesson on anesthesia (the next one, Clinical Cortex #8*: Anesthesia*). For our discussion here, we need only focus on two specific types because pain is transmitted either by **thickly myelinated**, **fast-conducting** type Aδ fibers or **unmyelinated**, **slow-conducting** type C fibers. Nociceptors in the periphery are activated by their unique stimulus (Motor and Sensory Tracts #2: *Sensory Systems*), and the sensory neuron depolarizes. There are two routes up the peripheral nerve—a fast fiber tract and a slow fiber tract.

The first-order sensory neurons of the **fast fiber tract** (officially, the neospinothalamic tract) use fast-conducting **Aδ fibers** and synapse on a second-order neuron immediately upon entering the spinal cord. The second-order neuron then crosses the midline and ascends the cord. The first-order neurons of the **slow fiber tract** (officially, the paleospinothalamic tract) use slow-conducting **C fibers** and synapse on neurons in nuclei, just medial to the nucleus of the fast fiber tract in the dorsal horn.

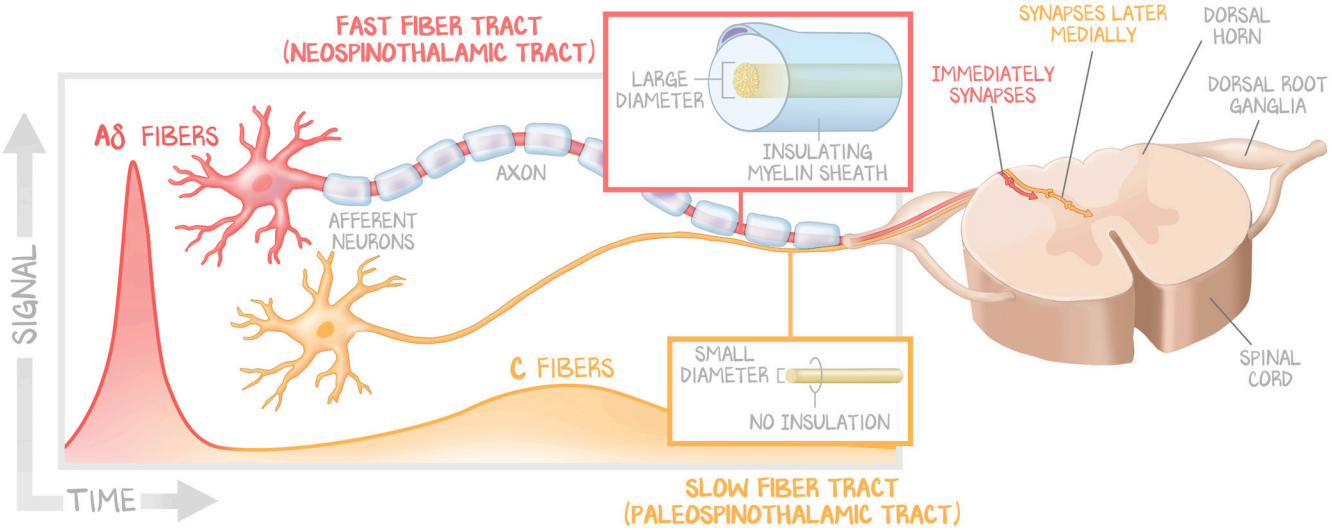

Figure 6.1: Sensory Fiber Types
Pain fibers come in one of two varieties—fast or slow. The fast fibers are type A fibers with heavy myelination and large axons. The fast fiber tract is type Aδ (A-delta) and quickly propagates the sensation of pain to the spinal cord. The slow fiber tract is made up of type C fibers, which are unmyelinated and have a narrow axon diameter. The skin receptors that depolarize both type C and type Aδ fibers are the same—the same noxious stimulus will activate both. Type C fibers have a slower conduction velocity and transmit the receptor activation to the spinal cord slower than type Aδ fibers. The spinothalamic tract is myelinated within the central nervous system, so it is the conduction velocity in the peripheral nerve that separates the two tracts.

The neurons in the spinal cord that will receive the signal from the first-order sensory neurons of the **fast fiber tract** are present immediately upon entering the dorsal horn. **Glutamate** (excitatory) is released, and the second-order neurons depolarize. Their axons cross the midline and ascend. All of the axons from the fast fiber tract go to the thalamus. Most of them go to the ventral posterolateral nucleus (VPL) of the **thalamus,** meeting the neurons of the DCMLS, and then continue on to the **primary somatosensory cortex**. This is the thing we have led you to believe is the one STT. Some of the fast fiber tract's axons synapse on neurons of the dorsal thalamus, which sends projections down to the brainstem (more on this next paragraph). The conduction velocity of fast fibers can get up to 60 m/s, and the conduction velocity within fascicles in the CNS is just as fast. The instant the noxious stimulus is encountered, the cortex knows. This enables the organism to react to the stimulus quickly and is what causes the sudden, most intense pain at its onset. It hurts the most the moment you stub your toe and, although it may still hurt, the remaining throbbing is certainly less than the initial stubbing. It hurt the most the moment you stubbed it because of the fast pain fibers. They are fast, but also brief. The toe continued to ache because the chronic pain tract, the slow fiber tract, hadn't caught up yet.

The arrangement of the **slow fiber tract** is quite different. First, C fibers are slow, with a conduction velocity between 0.5 and 2 m/s. C fibers are found in the peripheral nerves only; the fascicles of the CNS are myelinated, so the conduction velocity is the same as any other. Whereas the fast fiber tract has already informed the cortex of the stimulus, and the cortex has likely already taken steps to counteract the noxious stimulus (jerking your hand away from the hot stove), the pain along C fibers from the periphery hasn't even made it to the spinal cord. When the action potential reaches the spinal cord, there is no second-order STT neuron waiting for it. Instead, there are interneurons, sometimes as many as three in series (one after another) that lead to the second-order neuron whose axon crosses and ascends the spinal cord. The first synapse onto the first interneuron uses a neurotransmitter called **substance P**. Substance P is unlike glutamate. It is a depolarizing neurotransmitter, but one that requires accumulation in the synaptic cleft. The moment a noxious stimulus is encountered, substance P is released into the synaptic cleft, but there is no depolarization. As the noxious stimulus continues, more and more substance P accumulates, leading to depolarization. This system ensures the organism will remove itself from the noxious stimulus by increasing in intensity, becoming an unbearable pain.

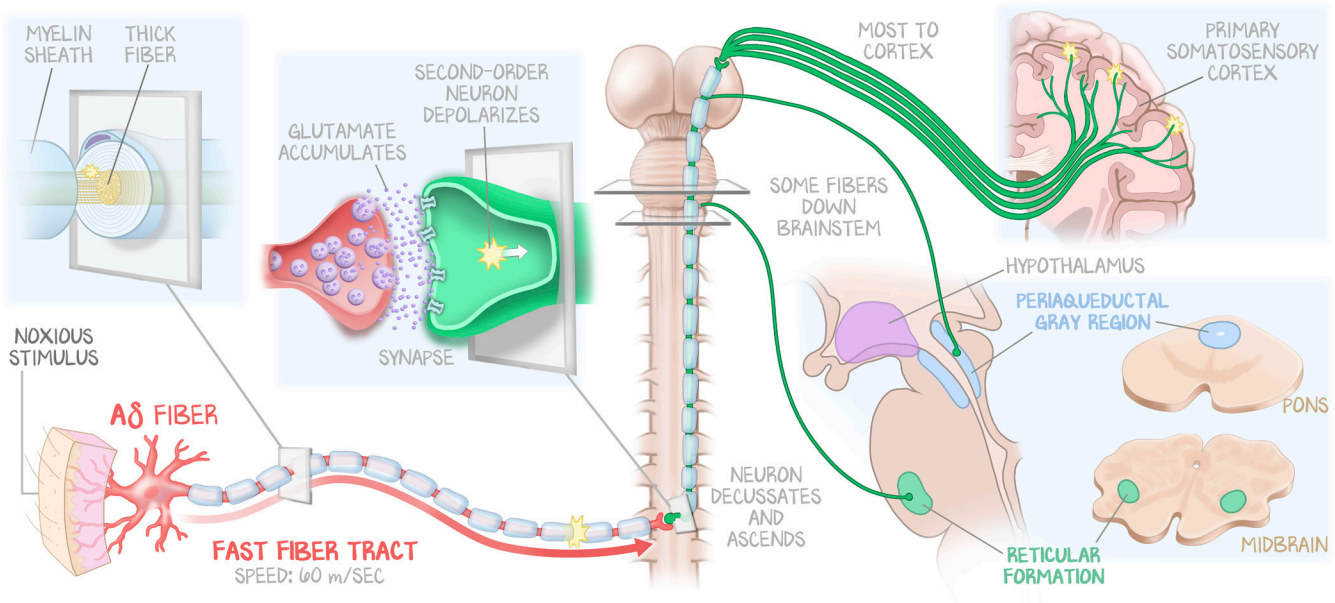

Figure 6.2: Fast Fiber Tract
The fast fiber tract is what you were probably thinking of as we taught you that the spinothalamic tract carries pain and temperature. Like the DCMLS (which has the most insulated, largest-radius axons and the fastest conduction velocity), fast fiber axons are myelinated and have large radii. The conduction velocity is fast, using glutamate as an excitatory neurotransmitter, and there is no interneuron between the sensory neuron's axon and the cell body of the second-order neuron, the axon of which will cross and ascend. The fast fiber tract primarily goes to the thalamus then to the cortex; it does have a few projections to the brainstem as well. It is the slow fiber tracts that introduce additional complexity in response to pain.

The fast fiber tract alerts the cortex to extreme pain. The slow fiber tract continues to let the cortex know there is still a noxious stimulus. And the longer it goes on, the stronger the slow fiber tract will be. But if the cortex moves the organism away from the noxious stimulus, and there are no more depolarizations from the periphery, but there is still a lot of substance P, then there can be ongoing pain that serves no utility. So, there must be a way to modulate the interneurons at the level of the spinal cord. We'll get there. But first, let's see where the slow fiber tracts end up.

Whereas the fast fiber tract primarily heads to the thalamus and then the sensory cortex, the axons of the slow fiber tract primarily terminate within the brainstem. Although some axons do continue on to the thalamus (how increasing substance P induces increasing pain), most of the axons will go to the **reticular formation** (a nebulously defined region that extends from the midbrain to the medulla), a series of nuclei just anterior to the top of the fourth ventricle of the pons, the **tectum** of the midbrain (posterior to the cerebral aqueduct, anterior to the colliculi), or the **periaqueductal grey** region surrounding the cerebral aqueduct of the midbrain. Without a map, that sounds complicated, but it isn't. Those things describe a very small region of interconnected structures as they relate to the midbrain and pons junction. Those are a lot of complicated words, but it just means "*goes to brainstem, synapses posteriorly, near the cerebral aqueduct.*" From the brainstem synapses, multiple short tracts send signals to the **thalamus**, hypothalamus, and analgesic nuclei in the midbrain (more on this in a bit)

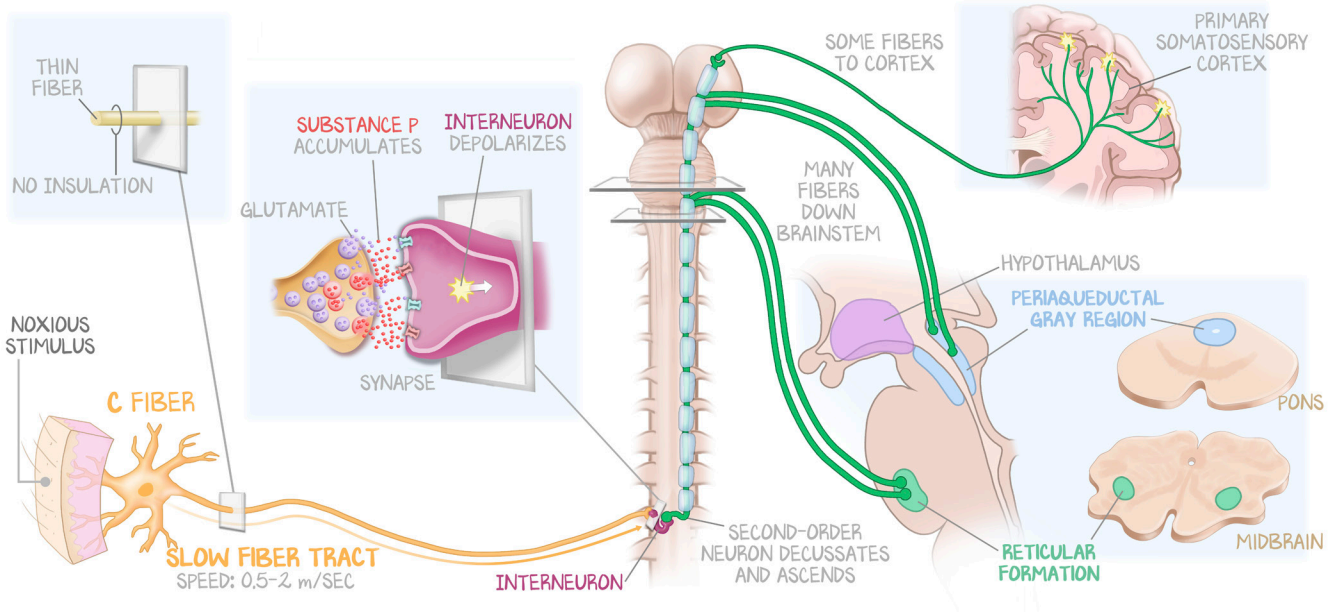

Figure 6.3: Slow Fiber Tracts
We fibbed a little in Figure 6.1. The slow fiber tracts are slow because they have unmyelinated axons and, therefore, no myelin insulation. But they differ from the fast fiber tracts in many ways. First, there are interneurons in the spinal cord—sometimes only one, sometimes a few—between the sensory neuron's synapse and the final neuron of the spinothalamic tract that will cross and ascend. The synapses through the interneurons sometimes involve substance P rather than glutamate. Substance P requires the accumulation of the neurotransmitter to initiate depolarization of the postsynaptic neuron. Substance P accumulates when the noxious stimulus is ongoing. And then there is the destination—the slow fiber tracts do transmit to the cortex (chronic pain hurts). But it mostly goes to the brainstem, synapsing on the tectal (posterior) periaqueductal grey and the reticular formation in the pons. Slow pain fibers go to the brainstem, induce suffering, and are paired with the analgesia tract, below.

These brainstem innervations appear to be important for the **suffering** of pain, as was demonstrated in animal models. Pain signals were blocked from reaching the cerebrum (by transecting the midbrain) so that no somatic pain could be felt, and yet the animals' bodies had undeniable evidence of suffering when any part of the body was traumatized. In addition, electrical stimulation where the slow fiber tracts terminate—the reticular formation of the brain stem and intralaminar nuclei of the thalamus—has a strong **arousal effect** on nervous activity throughout the brain. This explains why it is almost impossible for a person to sleep when he or she is in severe pain.

The Analgesic Tract

Just as pain fibers rise up from the periphery and synapse on the thalamus and then the cortex, the pain tract rises from the periphery, synapses on the thalamus, and then the cortex. But the pain tract also projects to the brainstem, where there are synapses with the brainstem in nuclei located posterior to the cerebral aqueduct in the midbrain and somewhat in front of the fourth ventricle in the pons. There are also analgesic tracts that descend from the same region—the floor of the third ventricle and anterior brainstem, anterior to the cerebral aqueduct. The analgesic tract modulates that tract and **inhibits pain** interneurons at the synapse—**in the spinal cord**. Inhibiting pain is the same thing as **providing analgesia.** This is how the brainstem can determine if the noxious stimulus is removed and if the ongoing pain is needed. If not, the analgesic tract turns it off.

See the **analgesic tract** as an **inhibitor motor** tract of the sensory system called the pain tract. The analgesic tract is outside of cortical control and is involved with pain sensory input. These neurons are silent when there is no active pain signal coming up from the periphery. But when noxious stimuli

depolarize the pain sensory tracts, the second-order neurons go to the midbrain and synapse on third-order neurons located posterior to the spinal canal, which then project all over the brainstem. The analgesic tract originates from the **periventricular nuclei** of the **hypothalamus** (on the anterior side of the cerebral aqueduct, just under the third ventricle). First-order neurons descend to the midbrain, where they **synapse on second-order neurons** in the **periaqueductal grey** anterior to the cerebral aqueduct, right in front of where the slow fiber tract second-order neurons synapse.

Those second-order neurons from the anterior periaqueductal grey are **enkephalin neurons** (more on enkephalin in the next section), which project to the **raphe nucleus** (also nucleus raphe magnus) and the **reticular nucleus** (reticular formation, nucleus reticularis paragigantocellularis) in the medulla. You did just see that above; it's the region of the brain where the pain sensory tracts synapse. Electrical stimulation of the periventricular nucleus, periaqueductal grey, or raphe nucleus can eliminate the perception of pain. The final descending axon from the raphe nucleus crosses with other descending (motor) fibers in the medullary pyramids and synapses on an **interneuron** in the **posterior horn** of the spinal cord at the exact level the pain signal is coming from. The interneurons are **stimulated** by the release of **serotonin** by the axon terminals of third-order neurons from the raphe nucleus (which is responsible for the greatest amount of serotonin in the brain, and this is not the only place its axons go). The interneuron, also an enkephalin neuron, releases **enkephalin**, inhibiting the neurons that transmit the pain signal.

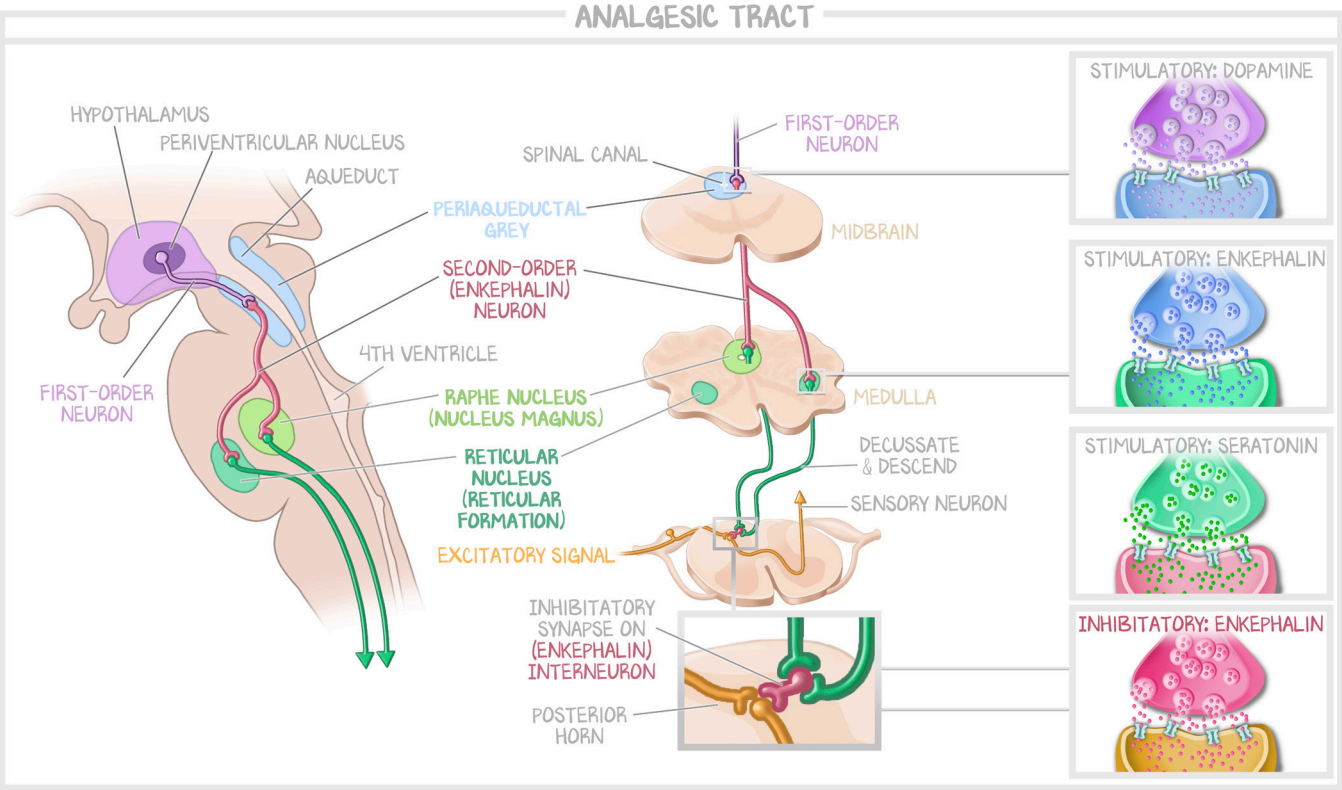

Figure 6.4: Analgesia Tract
Originating from the periventricular nuclei of the hypothalamus, the analgesic tract utilizes enkephalin-secreting interneurons to limit the transmission of pain from the periphery. The analgesic tract mitigates the sensation of pain by inhibiting the presynaptic and postsynaptic neurons, the depolarization of which results in the perception of pain (both by cortex and the brainstem). Hypothalamic axons project to the tegmental (anterior) periaqueductal grey and release dopamine, stimulating an enkephalin-secreting interneuron. That interneuron releases enkephalin in the reticular nucleus and raphe nucleus of the pons, stimulating the serotonin-releasing neurons in those nuclei. The serotonin-releasing neurons' axons descend the spinal cord to synapse on and stimulate yet another enkephalin-secreting interneuron. The axon of this interneuron is minuscule and releases enkephalin into synapses at its spinal level. How enkephalin works comes next.

What happens in the brainstem is poorly elucidated. What happens in the spinal cord is well elucidated. The interneurons, stimulated by serotonin neurons from raphe nucleus, release enkephalin. Enkephalin is an endogenous opioid neurotransmitter. This hyperpolarizes the interneurons and the second-order neuron of the STT. If the interneurons of the slow fiber tract are prevented from depolarizing, the signal will not be sent to the cortex or brainstem.

Thus, although the details of the brain's opioid systems are not yet completely understood, we can generally say that **activation of the analgesia motor system** by nervous signals entering the periaqueductal grey and periventricular areas, or **inactivation of pain sensory pathways** by morphine-like drugs at the spinal cord, can almost totally suppress many pain signals entering through the peripheral nerves.

Cellular Mechanisms of the Analgesic Tract

For many brainstem structures, medical science has elucidated the output of the nuclei but not necessarily the intracellular mechanisms of the cells of those nuclei. Like the neurons of the nuclei they are in, the opioid receptor's intracellular mechanism hasn't been fully elucidated, especially in response to developing tolerance. Here's what is pretty well established.

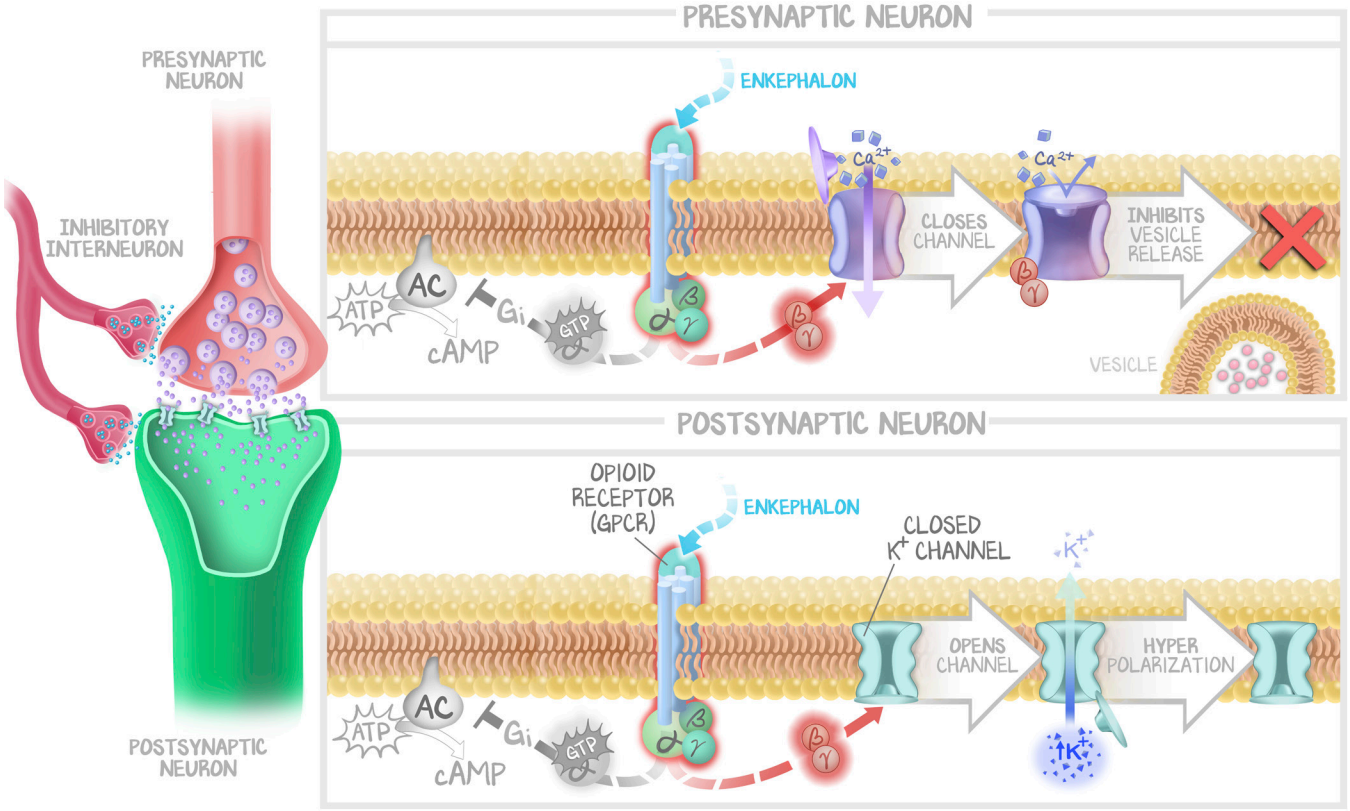

Figure 6.5: Opioid Receptors are GPCRs with a Twist
Other GPCRs have an active βγ dimer, although we haven't taught you any except GABAB and now opioid receptors. The mechanism of action is through the Gi α-subunit, just as always (inhibition of adenylate cyclase, reduction in cAMP). But there is a second mechanism of action through the βγ dimer, which closes calcium channels on the presynaptic neuron (reducing the amount of excitatory neurotransmitter released) and opens potassium channels on the postsynaptic neuron (acting as an inhibitory postsynaptic potential).

The **opioid receptors** are GPCRs that use the G_i α-subunit. The G_i α-subunit does what you've seen it do over and over throughout this course—inhibit adenylate cyclase, thereby decreasing the formation of cAMP, inhibiting downstream phosphorylation of proteins via PKA, and inhibiting modulation of gene transcription by CREB. That effect is likely what regulates the opioid receptor and is involved in the development of tolerance.

But also, opioid receptors are present on both presynaptic glutamate-secreting neurons and postsynaptic opioid receptors. In both cases, G_i inhibits adenylyl cyclase. In addition, on the presynaptic side, the βγ subunit (that we have taught you always to ignore) binds to and prevents the opening of the voltage-gated calcium channel, preventing depolarizations from resulting in exocytosis. On the postsynaptic side, the βγ subunit opens potassium channels, which allow potassium out of the cell, hyperpolarizing the postsynaptic cell.

Presynaptic voltage-gated calcium channel inhibition reduces the release of excitatory neurotransmitters (glutamate of substance P). **Postsynaptic potassium channel** activation hyperpolarizes the postsynaptic cell. All the while, some yet to be elucidated effect of decreasing cAMP further hyperpolarizes both cells. This is what $GABA_B$ receptors do, and why we didn't discuss $GABA_B$ receptors very much in that lesson. This is where we want you to learn it.

Opioid receptors and Endogenous Opiate Neurotransmitters

There are three main receptor types—μ, δ, and κ.

μ (Mu) opioid receptors (MOR) bind to the endogenous ligands, β-endorphin and endomorphins 1 and 2. The proopiomelanocortin (POMC) that generates melanocyte-stimulating hormone in keratinocytes and ACTH in the anterior pituitary is the same POMC that generates endorphins. There are three subtypes. The **μ_1 receptor** is responsible for **analgesia.** The **μ_2 receptor** is not only vital for **euphoria** but is also causes all of the major consequences of opioid drug use—**respiratory depression** (breathe so slowly they turn blue from hypoxemia), **miosis** (pinpoint pupils that do not dilate), and **opiate-induced** constipation. The **μ_3 receptor** causes vasodilation. MOR are also responsible for the **dependence** and **tolerance** that are seen in opiate medication use. Activation of these receptors effectively eradicates the sensation of pain (spinal cord and thalamus synapses), the suffering from pain (brainstem synapses), and euphoria (unclear and relatively nebulously midbrain).

δ (Delta) opioid receptors (DOR) bind to **enkephalins** (met-enkephalin and leu-enkephalin). They play a role in **analgesia**, especially at the level of the spinal cord, as discussed above.

κ (Kappa) opioid receptors (KOR) bind to **dynorphins** A and B. They provide analgesia, diuresis, and dysphoria. They are found in the CNS and PNS. They prevent the transduction of the pain signal, but they cause **dysphoria**. This isn't the opposite of euphoria; it is a vague sensation of not feeling well. When developing pain medications, minimizing the KOR effect is the goal.

Nociceptin opioid receptors (NOR) bind a ligand that was discovered by two groups simultaneously. One named the ligand **nociceptin** (thus the convention of nociception opioid receptor), and the other named it orphanin FQ. Nociceptin won. Be careful; this is not a ligand for nociceptors in the skin. Nociceptin is a ligand for NOR found in the CNS. Even though it is structurally similar to the opioid receptors and a GPCR that acts through G_i, it appears to have the opposite effect as opioid receptors—hyperalgesia, increased gastric motility, no reward modification. Further, nociception has little affinity for opioid receptors, and endogenous opiate signaling has little affinity for NOR. Likely, it represents genetically similar ligand receptor pairing that coincidentally overlaps with NOR.

MOR	DOR	KOR	NOR
Endorphins	Enkephalins	Dynorphins	Nociceptin
μ_1 = analgesia μ_2 = euphoria μ_3 = doesn't matter	Analgesia in the spine, analgesia motor tract	Analgesia, but can also lead to dysphoria	Not an opioid receptor, causes hyperalgesia, arousal, increased gastric motility
μ_2 causes miosis, respiratory depression, constipation, and addiction			

Table 6.1: Opioid Receptor Subtypes

Opioid Receptor Agonists

Some opioid agonists activate the MOR in the CNS so weakly that they are used to treat **diarrhea**. The only agents we have to slow down diarrhea are opiates with strong agonism of MOR in the gut. The side effect of most opioids is constipation. The intended effect of **loperamide** is to slow diarrhea. Take too much, and there will be opiate-induced constipation.

MOR agonists that are slightly stronger but fail to stimulate the euphoric effects of other MOR agonists can be used as **cough suppressants**. Codeine, one of the naturally occurring compounds in the poppy flower (morphine and codeine are found in the flower's gum, although codeine is usually synthesized from morphine to be sold commercially), is used together or alone for cough prevention. It works by acting centrally to raise the cough threshold.

We are not going to discuss each opiate in detail. Once you cross the line from codeine into "anything above," you're talking danger-zone opiates. We are going to talk about morphine in detail, then throw up a table on the others. Danger zone means the "opiate abuse pandemic." There is absolutely appropriate opiate use for acute pain in an acute setting. But chronic use of acute medications, much like we saw with benzos and especially when used for the euphoria rather than the analgesia, leads to dependence and tolerance.

Morphine. Morphine is the model. If you understand morphine, you understand them all. Morphine has many actions. The first are, of course, **analgesia** and **euphoria** (a general sense of wellbeing), which is all good. However, common side effects are **decreased respiration**, **miosis** (pinpoint pupils), and **constipation**. Because morphine causes analgesia and euphoria, it is convenient for the **treatment of acute pain** (duh). It also **decreases the fear of dying** (useful for palliation) and **alleviates dyspnea**. Those last two are likely to be the result of inhibiting the pain tracts to the brainstem, the suffering sensation of pain. But morphine carries another interesting use. It is commonly used to treat acute cases of **pulmonary edema** and **myocardial infarction**. Not only does it "chill the patient out" (decreasing sympathetic tone and cardiac demand), it also causes **venous dilation**, decreasing venous return and cardiac demand. Morphine is **rapidly absorbed** in the GI tract but undergoes **heavy first-pass metabolism** where it gets glucuronidated to a more water-soluble form (which is why it used to be given only IV).

It should not be used for a **head injury**, **acute pancreatitis,** or **bronchial asthma**. Well, why not? In head injury with respiratory depression, CO_2 accumulates, causing vasodilation and leading to increased edema. In pancreatitis, morphine is associated with the failure of the hepatopancreatic sphincter (sphincter of Oddi). In bronchial asthma, morphine exacerbates histamine response, thereby exacerbating the asthma. Obviously, because it is a vasodilator, states of **hypovolemia/**shock are also a general contraindication.

Morphine also has a high degree of dependence and tolerance. **Tolerance** is when one needs a higher concentration of a drug to experience its intended effect. This may be so severe that there is **no upper limit** for the recommended dosage, and it is solely dependent on the patient (10 mg may kill a person without exposure to morphine, whereas a 60 mg dose may not be enough to ease the pain of sickle cell crisis or cancer). Tolerance can develop to the analgesic, respiratory, and sedative effects of the drug, but NOT to the constipation or miotic effects. **Dependence** is characterized by the need to do something despite physical harm. Rats will suffer electric shocks in order to get their hit of morphine. Humans have physical dependence (withdrawal symptoms that include convulsions and vomiting) and psychological dependence.

Overdose with morphine causes a classic triad: **coma, miosis, and cyanosis** with eventual respiratory failure. The treatment for morphine overdose is an opiate antagonist, such as **naloxone** or **naltrexone**, that is given IV, has a short duration, and causes **immediate withdrawal symptoms**. Abusers of opiates will know naloxone as Narcan®.

DRUG	RELATIVE TO MORPHINE	NOTES
Fentanyl	100	Transdermal, intravenous for induction of anesthesia, lollipop preparations; the most addictive potential
Methadone	5–10	Long onset and duration, used to treat opioid abuse
Hydromorphone	5	Higher-potency morphine, used inpatient
Oxycodone	1.5	Provided with acetaminophen to reduce the risk of injection Avoid with acetaminophen in liver failure or cirrhosis
Morphine	1	Extended-release BiD, immediate-release prn, intravenous hospital
Hydrocodone	2/3	Once considered a "lighter" version of oxycodone, the two are no longer considered the same, but carry the same schedule
Codeine	N/A	Cough Syrup
Loperamide	N/A	Diarrhea-treatment

Table 6.2: Relative Opiates and Some Notes

Opioid Receptor Agonists Used To Treat Opioid Abuse

Methadone. Methadone is an opioid that is given to abusers of opioids that wish to stop using. It has a **long half-life** and therefore a long time to onset and a long duration of action. It is safe to give to patients in long-term addiction recovery. The activation of MOR receptors reduce cravings, prevent withdrawal symptoms, but doesn't activate MORs enough to cause euphoria or sedation. The goal is to gradually wean the dose over time. This must be administered within a methadone clinic – under observation by medical professionals. Methadone still is an opioid so can be abused if taken in large amounts.

Buprenorphine. Buprenorphine is a **partial agonist of MOR**. No matter how much opioid drug (prescribed or elicit) the patient takes there is a new, lower ceiling of effect. Because buprenorphine is only a partial agonist, it will limit how much of an effect the exogenous opioid can have. And because it is a partial agonist, it also treats cravings, withdrawal symptoms, and doesn't cause sedation or euphoria. In addition, buprenorphine antagonizes DOR and KOR, satisfying cravings caused by empty MOR, but without inducing analgesia, limiting the risk for relapse.

Opioid Receptor Antagonists

Naloxone. Naloxone antagonizes **most opioid receptors** with high affinity. Its chemical compound differs from that of morphine by a methyl group and a hydroxyl group. Despite its higher affinity for opioid receptors, it is shocking to find that it is a **near-instantaneous pure antagonist**. Patients die of an opiate overdose because of respiratory depression. When a patient needs reversal—cyanosis, sedation, respiratory depression, and pinpoint pupils—naloxone is used emergently to **reverse coma and respiratory depression**. However, because it reverses all opioid receptors at once, it puts the patient into rapid withdrawal—pain, vomiting, pain, itching, something else, pain, and more pain.

Naltrexone. This is an **orally effective, longer-acting** naloxone. Naltrexone does not activate MOR receptors so cannot be used in the early phases of treatment as it will not treat cravings or withdrawal symptoms.

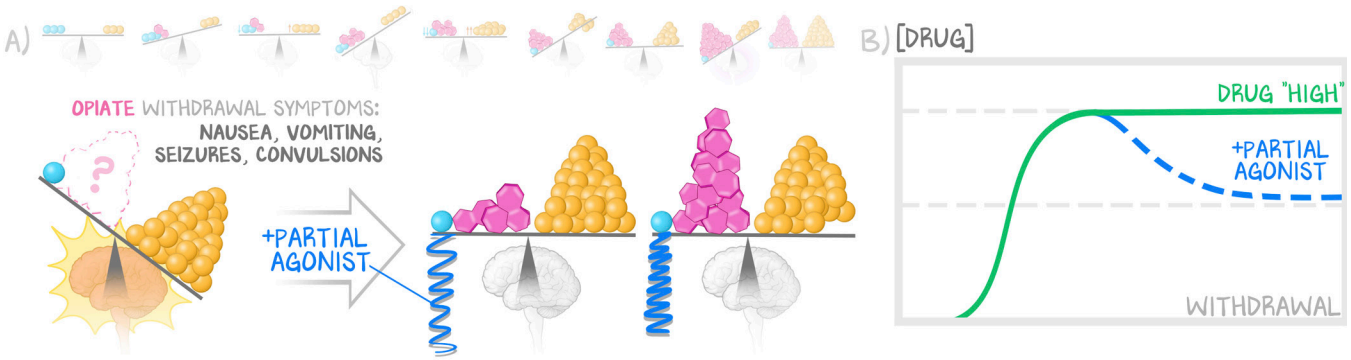

Figure 6.6: Withdrawal and Partial Agonists
Partial agonists activate the receptors enough to abate withdrawal symptoms but prevent activation to full effect. Acting like a spring on the seesaw model, when there is no drug around, the spring lengthens, preventing overexcitation and withdrawal. If a patient tries to get the benefit of the drug with the partial agonist present, the spring resists and prevents the effect of the drug. This is a play on partial antagonism from General Pharmacology, where we used terms like V_{max} in place of "drug effect." Same concept, different language.

Warning Against Pharma. A popular agent on the market is Suboxone, the trade name for the combination of buprenorphine and naloxone. Think about that for a minute. What does oral naloxone do? Not naltrexone, oral naloxone. It enables pharma to productize, patent, and maintain a Market Exclusivity Period on a drug (buprenorphine/naloxone) whose only meaningful active ingredient—buprenorphine—has long since fallen out of patent, its MEP long since expired. But Suboxone was sneaky—it sounds like naloxone, naltrexone, and methadone. It feels like a generic name, like something special. Buprenorphine has been around since the 1970s. Suboxone first appeared in the US in 2002, with an MEP that ends in 2022. And we fell for it. We didn't even consider how absurd it was, and naturally allowed ourselves (the authors of these notes) to see Suboxone (oral naloxone doesn't do anything) as buprenorphine with naltrexone (oral naltrexone does work). Oral naltrexone with buprenorphine is actually the much less popular drug Sublocade. Suboxone represents one of the dangers of the pharmaceutical industry—marketing and branding work on patients, doctors, and educators alike.

Consumers paid a huge price . . . the pharmaceutical industry essentially hiked the price of a Trade Name drug whose only effective medication was a generic. What good came of it? Maybe patients perceived Suboxone as having less stigma than methadone, and therefore became more willing to undergo treatment, thus saving lives. So maybe, MAYBE patient acceptance of Suboxone was worth the all the dollars the pharmaceutical industry effectively stole by rebranding an old drug with a new name and higher price.

The FDA-mandated packaging insert, the thing the FDA had access to when approving this "new" trade drug, gives all the information necessary to see the sham: buprenorphine has a mean elimination half-life from plasma of 37 hours. Naloxone has a mean elimination half-life from plasma of 1.1 hours. In other words, at once-daily dosing, the naloxone cannot be effective in any way. In other words, "we added nothing to buprenorphine; we're treating patients with buprenorphine; thanks for the money!"

What's next? Buprenorphine, naloxone, and 3% saline? "We recommend you mix with three parts water" (bringing it back down to about 0.9% saline). New formulation, new MEP!

Non-Opioid Pain Medications

Ketorolac. This is an NSAID that is as **effective an analgesic as morphine**. It can be given as a subcutaneous injection once a month. It is an uber NSAID used to treat pain. Don't mix ketorolac with over the counter NSAIDs.

Tramadol. This is a **centrally acting analgesic** that is **not an opiate**. The mechanism is unknown, but we know it has at least some opioid activity because its effects are only **partially blocked by naloxone**. There is an increased risk of seizures when naloxone is administered for overdose, but it is a good and valuable tool for treating moderate to severe pain.

Use opiates for excruciating pain, these non-opioid drugs for moderate-to-severe pain, and regular NSAIDs or acetaminophen for mild-to-moderate pain.

Mechanisms of Tolerance Are Not Well Elucidated

Patients who are on chronic opiates will eventually need to increase their dose. The goal is to get your patients off opiate medications. If that can't happen, tolerance will develop. There are many good ideas as to how opioid receptors are regulated, but none have been proven. Thus, nothing in this section can be tested on a licensing exam, and we're not sure it's correct. But here's the evidence.

Chronic opioid administration has a propensity to lead to irreversible dysfunction of the endogenous opioid system. Like with everything else, if you don't use it, you lose it. Because morphine is such a potent opiate agonist, and most physiological systems have physiological feedback antagonism, exogenous stimulation of opioid receptors results in a reduced need for endogenous opioids. The inability of the endogenous opioids to react appropriately to outside stressors will cause users to ultimately become dependent on exogenous opioids to mimic the action elicited by the endogenous opioid system.

But something else has to be happening. Increased concentrations of cAMP have been observed in cells that are exposed to morphine for prolonged periods. This may be the result of adaptive cellular changes through increased adenylyl cyclase activity and possibly other mediators of the pathway.

β-Arrestins, which are involved in receptor recycling, have also been associated with the desensitization of opioid receptors. In in vivo studies, arrestin β2 knockout mice failed to develop analgesic tolerance to chronic opioid administration. This indicates that it isn't just a decrease in endogenous opioid synthesis, but also the downregulation of the number of receptors on the cell surface. The initial endocytosis requires arrestin β2.

There is also this concept of biased agonism. The β-arrestins both induce the internalization of the receptor and control its fate. But each opioid—endogenous or exogenous—has varying patterns with the same receptor. An opioid is not simply interchangeable with any other opioid. Functionally, that is the case. Cellularly, however, it may not be. In one study, after prolonged exposure to morphine, *JNK* (a type of kinase) knockout mice did not develop tolerance (i.e., no internalization), whereas *GRK3* (another

kinase) knockout mice developed typical tolerance. In contrast, after exposure to synthetic fentanyl, the *GRK3* knockouts did not develop tolerance, whereas the *JNK* knockouts did.

Those were kinases, right? It is already known that chronic exposure to opioids, either exogenous or endogenous, leads to receptor phosphorylation on specific amino acid residues in the intracellular C-terminus. Receptor phosphorylation recruits arrestin molecules, which ultimately decide the fate of the G protein-coupled opioid receptor.

So it looks like the overactivation of opioid receptors may lead to low cAMP levels, PKA activity, and CREB. The product of that has nothing to do with opioid receptors. But another unrelated mechanism that utilizes AC-cAMP-PKA-CREB within the same cell has its own feedback loop that corrects the cAMP levels in the presence of stimulated opioid receptors. Kinases are upregulated and do what they are supposed to do—phosphorylate the opioid receptor. This marks it so the arrestin molecules can internalize it. If the receptor is phosphorylated one way, it is marked for degradation. If the receptor is phosphorylated another way, it is recycled. The trouble is that not every cell with opioid receptors behaves the same way, and every opioid induces a different intracellular response.